Nutritional Intake Patterns of Patients with Chronic Venous Leg Ulcers

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Chronic venous leg ulcers (CVLUs) are challenging conditions affecting approximately 1% of the population and 3.6% of individuals over age 65 years, costing the U.S. healthcare system up to $3.5 billion annually. Certain nutritional deficits are linked to poor wound healing. For example, high n-6/n-3 polyunsaturated fatty acids (PUFAs) ratios are associated with chronic inflammation which may delay healing progression. Thus it may be important to assess diets of CVLU patients to ascertain whether nutritional interventions are warranted. This study's purpose was to determine average daily intake of key nutrients known to impact wound healing in a sample of CVLU patients. **Sample**: 12 adults from the Midwest with CVLUs, ages 48-80 years. **Method**s: Electronic Food Frequency Questionnaires (FFQs) were completed by participants during a onetime visit to a clinical research center to determine average daily nutrient intake for the previous three months. Plasma samples were collected to quantify n-6/n-3 PUFA ratios and body mass indices (BMI) were calculated for assessment of overweight and obesity. **Results**: On average, according to recommended daily intake (RDI) parameters, participants consumed adequate amounts of zinc: 10.78 mg/d (*SD= 5.17*) (RDI: 8-11mg/d) and protein: 71.37g/d (*SD= 31.32*) (RDI: 46-56g/d), but lower than recommended amounts of vitamin C: 60.03 mg/d (*SD=49.73*) (RDI: 75-90 mg/d). Furthermore the average n-6/n-3 PUFA ratio was 11.25 (*SD= 1.99*) (optimal: 4:1) and the average, BMI was 41.48 (*SD=11.47*) (obese). **Conclusion**: Although CVLU patients in this study were consuming adequate amounts of zinc and protein, their vitamin C intake was lower than recommended, which could negatively impact wound healing processes. The high n-6/n-3 ratios suggest a pro-inflammatory state which could also contribute to healing delays. Additionally, high BMIs may increase other chronic disease risk. A multidisciplinary approach that promotes healthy, nutrient-rich diets may improve wound healing and long-term health outcomes in this population.

I. Statement of the Problem

Introduction

Chronic venous leg ulcers (CVLUs) are challenging clinical problems creating significant socioeconomic burdens for patients, families, and the healthcare system. Approximately 1% of the general population and 3.6% of those over the age of 65 are being treated for CVLUs (Moor, Vachon, & Gould, 2009). Moreover, because CVLUs are associated with aging the global incidence of CVLUs is predicted to escalate dramatically in future years (Hankin, Knispel, Lopes, Bronstone, & Maus, 2012). Current annual CVLU treatment related costs to the U.S. health care system alone are estimated to be between $1.5-3.5 billion and these costs are directly related to the time it takes for CVLUs to heal. Unfortunately, only 50%-65% of CVLUs heal within 6 months, 20% remain unhealed after 2 years, and approximately 8% remain unhealed at after 5 years (Hankin et al., 2012). Thus, innovative, cost-effective adjunct treatment strategies are needed to facilitate healing of these problematic wounds.

The pathobiology of CVLUs involves sustained venous hypertension, high levels of activated pro-inflammatory cytokines, and excessive neutrophil-derived proteases in the microenvironment that collectively result in chronic inflammation (Hankin et al., 2012). Although inflammation is an important initial step in the wound healing process, chronic inflammation prevents or delays subsequent healing stages (Raffetto, 2013). Certain nutrients such as vitamin C, zinc, protein, and the amino acids glutamine and arginine are known to be essential for efficient wound healing. Other nutrients such as n-6 and n-3 polyunsaturated fatty acids (PUFAs) play are involved in inflammation regulation and thus may contribute to chronic inflammation and poor healing if not consumed in relatively balanced ratios. However, little is known about the intake patterns of these nutrients in patients with CVLUs. Thus, assessing the

average daily intake patterns in a sample of CVLU patients and comparing them to recommended daily intake (RDI) levels will begin to address this gap in knowledge and help determine if nutritional interventions could potentially improve outcomes.

Background

Wound healing is an intricate process involving several stages beginning with vasoconstriction, hemostasis, and inflammation (MacKay & Miller, 2003). The goal of wound management is to facilitate healing using evidence based interventions such as compression therapy, the gold standard for CVLU care. Additionally, for wound healing to be successful, adequate nutrients and blood must be supplied to the site of tissue damage. Thus a patient's overall health and nutritional status influence wound healing outcomes (MacKay & Miller, 2003). Several studies have reported that an inadequate consumption of specific nutrients such as vitamin C, zinc, protein, amino acids, and certain PUFAs leads to poor healing in patients with pressure ulcers (Gray & Whitney, 2003; Heyman, Van De Looverbosch, Meijer, & Schols, 2008; Langer, Schloemer, Knerr, Kuss, & Behrens, 2003; Legendre et al., 2008; MacKay & Miller, 2003). However, a paucity of studies has evaluated these nutrients in patients with CVLUs. Furthermore, patients with chronic wounds often have an increased metabolism due to high levels of systemic inflammation and increased cellular activity at wound sites (MacKay & Miller, 2003). Therefore, patients with chronic wounds such as CVLUs may actually require a higher than normal intake of certain nutrients to expedite healing (MacKay & Miller, 2003).

Vitamin C, zinc, protein, and amino acids are the nutrients reported to be especially important to wound healing processes. Vitamin C is important for the synthesis of connective tissue throughout the body. Therefore, an inadequate consumption of vitamin C can lead to diminished fibrous tissue strength and an increased risk for wound dehiscence (MacKay & Miller, 2003).

Zinc aids in tissue regeneration and collagen formation because it facilitates the synthesis of DNA and RNA (MacKay & Miller, 2003). Amino acids are the building blocks of protein which are crucial to tissue regeneration and immune function (MacKay & Miller, 2003). Specifically, the amino acid glutamine is important for cell proliferation and serves as a source of energy for inflammatory cells. The amino acid arginine promotes immune function and thus helps prevent infection at wound sites (MacKay & Miller, 2003).

In addition to the commonly known nutrients associated with efficient wound healing, recent studies have suggested that an increased consumption of n-3 PUFAs may have positive effects because of their anti-inflammatory actions (Simopoulos, 2008). Unfortunately, Western diets are low in n-3 PUFAs relative to n-6 PUFAs (McDaniel, Massey, & Nicolaou, 2011) and because n-6 PUFAs have stronger pro-inflammatory actions than n-3 PUFAs, high n-6/n-3 PUFA ratios are indicative of high levels of inflammation (McDaniel et al., 2011) . Importantly, chronic inflammation systemically and locally at wound sites prevents progression of subsequent healing stages. Thus, manipulating PUFA levels through dietary interventions may be an effective method to reduce inflammation and improve CVLU healing outcomes. However, before clinicians can make definitive nutritional recommendations for CVLU patients, additional research is needed to evaluate the dietary intake patterns and opinions about taking nutritional supplements in this population.

Purpose

The purpose of this study was to test the hypotheses that CVLU patients 1) consume less than recommended daily intake (RDI) levels of nutrients known to be vital to wound healing (vitamin C, zinc, protein, and the amino acids glutamine and arginine), and 2) consume higher levels of n-

6 PUFAs relative to n-3 PUFAs. This study also assessed participants' opinions about making dietary changes and/or consuming nutritional supplements for the purpose of improving wound healing.

Significance

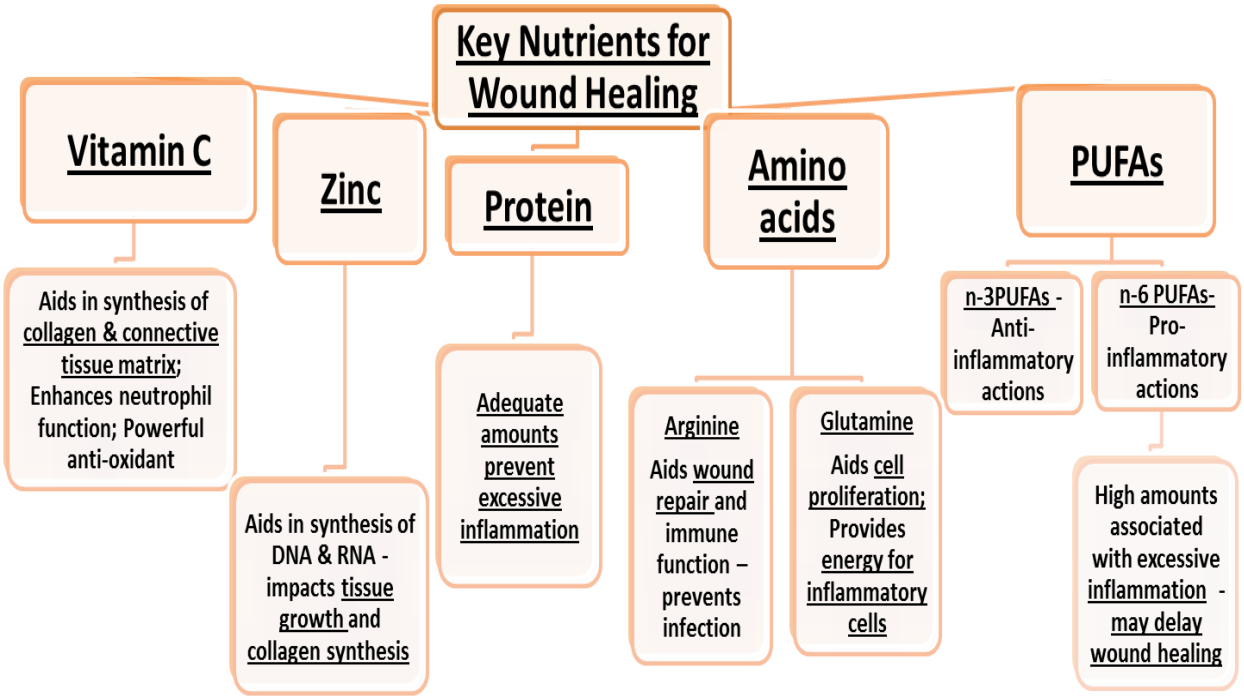
Chronic venous leg ulcers are costly for patients, families and the healthcare system because they require protracted treatment regimens. Furthermore, CVLU patients often have one or more chronic disease (e.g. Type 2 diabetes) contributing to wound healing delays. As a result of the collective health issues, CVLU patients frequently report feeling depressed and that their quality of life has diminished (Phillips, Stanton, Provan, & Lew, 1994). A nutrient dense diet containing the RDI of essential vitamins, minerals and trace elements is important for efficient wound healing, disease prevention and optimal health. Thus a dietary assessment may be an important first step in determining whether certain CVLU patients would benefit from making dietary changes or consuming nutritional supplements to not only facilitate wound healing, but to improve their overall health status.

CVLUs are frustrating for the patient and healthcare team because they are so challenging to treat and often recur. If dietary assessments and subsequent dietary counseling lead to improved healing outcomes for CVLU patients then the financial and emotional burdens could be reduced for all involved. Nurses are key members of the healthcare team who could facilitate the nutritional assessment/counseling process for CVLU patients in all settings including hospitals and extended care facilities. Nurses could also reinforce the importance of following the dietary recommendations and explain their link to wound healing and optimal health.

Theoretical framework

The theoretical framework used to guide the design of this study was adapted from the work by MacKay and Miller (MacKay & Miller, 2003) and McDaniel, Massey and Nicolaou (McDaniel et al., 2011).

Model 1. Key Nutrients for Wound Healing



The Transtheoretical Model of Behavior Change by James Prochaska was used to design questions to elicit patients' opinions about dietary supplements for the purpose of improving wound healing (Center for Substance Abuse Treatment, 1999). This theoretical model emphasizes five phases of behavior change including 1) pre-contemplation during which an individual is avoiding the issue and not thinking about making any changes; 2) contemplation during which an individual has acknowledged that there is a problem and he or she is weighing

the pros and cons of making a change to correct the problem; 3) preparation during which an individual begins to make steps to lead up to a behavior change; 4) action during which an individual actually makes the change in behavior; and 5) maintenance during which an individual maintains the behavior change and positive results are beginning to be recognized (Center for Substance Abuse Treatment, 1999). In this study, participants were asked if they would consider taking a nutritional supplement if there was strong evidence supporting its effectiveness to facilitate wound healing. They were also asked if there were any factors that would encourage or discourage them from taking such a nutritional supplement. Thus these questions assessed the stages of behavior change in this sample of CVLU patients.

Research Questions

The current study was designed to answer the following research questions in a sample of participants ages 48-80 years with CVLUs: (1) What are the average daily intake levels of key nutrients important to wound healing (vitamin C, zinc, protein, and the amino acids glutamine and arginine) and how do they compare to daily RDI levels? (2) What are the average plasma levels of n-6 PUFAs relative to n-3 PUFAs? (3) What are participants' opinions about making dietary changes and/or consuming dietary supplements to improve wound healing and overall health?

Limitations

Limitations of this study include a small sample size and a single data collection point. Also, this study's sample consisted primarily of White CVLU patients from the Midwest. These factors limit the generalizability of the findings because studies have reported significant variability in dietary patterns across races and in different regions of the country.

II. Review of Literature

Numerous research studies over the past ten years have evaluated relationships between nutrition and wound healing in humans with diabetic wounds and/or pressure ulcers, but few have included individuals with CVLUs. The studies reviewed suggest that an adequate consumption of vitamin C, zinc, protein, the amino acids arginine and glutamine, and n-3 PUFAs have positive effects on wound healing. However, the average American diet is high in calories, total fat, saturated fat, added sugar, sodium, and refined grains, and low in n-3 PUFAs, fiber, whole grains, and fruits and vegetables, which are rich in vitamin C, zinc, and phytonutrients (Cope, 2007). Therefore, it is reasonable to suspect that many patients with CVLUs are not consuming adequate levels of key nutrients associated with efficient wound healing.

Vitamin C And Wound Healing

Vitamin C is perhaps the most studied nutrient germane to wound healing. Vitamin C is necessary for the synthesis of collagen and other components of the "intracellular" matrix of connective tissues including bones, skin, and capillary walls (MacKay & Miller, 2003). Alterations in the intracellular matrix can lead to cutaneous lesions, poor adhesion of endothelium cells, and decreased tensile strength of fibrous tissue. Vitamin C also facilitates the function of neutrophils which serve as the chief line of defense against infection and tissue injury. Moreover, vitamin C is a strong, natural antioxidant, which helps to prevent or delay cell damage by inactivating free radicals before they enter cell membranes (Huether & McCance, 2008). It is recommended that healthy adult women ages 19 and older consume approximately 75mg/d of vitamin C and healthy adult men ages 19 and older consume 90mg/d (Food and Nutrition Board, Institute of Medicine, National Academies & U.S. Department of Agriculture,

National Agricultural Library, 2013). However, there are no recommendations for vitamin C intake for individuals with chronic wounds.

Several studies reviewed focused on the effects of supplemental vitamin C on the healing of pressure ulcers and reported positive findings. For example, a study by Taylor, Rimmer, Day, Butcher, and Dymock (1974) reporting that 500 mg/d of ascorbic acid (vitamin C) given 2x/day for up to 12 weeks resulted in a statistically significant mean reduction in pressure ulcer area when compared to baseline measurements (Taylor, Rimmer, Day, Butcher, & Dymock, 1974). Additionally, studies examining the effects of supplemental vitamin C on acute wound healing reported that healthy volunteers who ingested 1-3g/d of vitamin C for several weeks exhibited increased neutrophil function and lymphocyte transformation (Anderson, Oosthuizen, Maritz, Theron, & Van Rensburg, 1980). Another study suggested that a supplement of 1-2 g/d of vitamin C would be beneficial for pressure ulcer healing if started early in treatment (Levenson & Demetrio, 1992).

Although several studies noted a positive correlation between vitamin C supplementation and improved wound healing, other studies did not see significant change. For example, Riet, Kessels, and Knipschildn investigated the effects of ascorbic acid supplementation twice daily for the treatment of pressure ulcers and reported no healing improvement with high doses (ter Riet, Kessels, & Knipschild, 1995). They reported improved healing rates for the control group receiving only 10mg of ascorbic acid twice daily compared to the experimental group receiving 500mg of ascorbic acid twice daily and thus concluded that high doses of ascorbic acid did not facilitate the healing of pressure ulcers (ter Riet et al., 1995).

Similarly, Gray and Whitney examined the effects of vitamin C supplementation of 500mg 2x/day on pressure ulcer healing and reported that there was no improvement in healing rates

(Gray & Whitney, 2003). However, they did emphasize that higher doses of vitamin C may be needed for individuals under increased stress or for those who are vitamin C deficient. Vitamin C deficiencies can occur in those with chronic health issues, those who have experienced trauma, older individuals, those with cognitive deficits, and/or those with limited access to resources or adequate nutrition (Gray & Whitney, 2003).

Although the collective studies examining the relationship between vitamin C and wound healing in humans differ in their findings, the majority of the studies reviewed used a small sample size and focused only on pressure ulcers. Thus, additional studies are needed to examine the effects of vitamin C supplementation on other wound types such as CVLUs.

Zinc And Wound Healing

Zinc is essential for efficient wound healing because it plays an important role in the synthesis of DNA and RNA, which are needed for tissue growth and collagen synthesis (Health Quality Ontario, 2009). A deficiency of zinc can cause diarrhea, poor appetite, and a decreased sense of smell and taste (Health Quality Ontario, 2009) . Thus, zinc deficiencies may lead to an inadequate intake of other key nutrients that are important for efficient wound healing. The national daily intake recommendation for zinc is 11mg/day for healthy men ages 19 and older and 8 mg/d for healthy women ages 19 and older (Food and Nutrition Board, Institute of Medicine, National Academies & U.S. Department of Agriculture, National Agricultural Library, 2013).

Langer, Knerr, Kuss, Behrens, and Schlomer completed a meta-analysis of studies investigating zinc supplementation in patients with pressure ulcers (Langer et al., 2003). One study discussed how patients with pressure ulcers were given either 200mg of zinc sulfate 3x/day

for 24 weeks or a placebo (contents not specified) for the same interval of time (Norris & Reynolds, 1971). The patients taking the zinc supplement had a greater mean decrease in volume of pressure ulcer over time compared to the placebo group. The Medical Advisory Secretariat analysis also discussed zinc intake patterns in patients with pressure ulcers (Health Quality Ontario, 2009). One study within this analysis reported "that up to 88% of eating-dependent nursing home residents had dietary zinc intake levels below 50% of the recommended daily allowance" (Posthauer, 2006). Houston et al. reported that a group of individuals with pressure ulcers (stage III and IV) consuming 440mg/d of zinc sulfate for 30 days had significantly greater decreases in pressure ulcer volume than the group receiving similar care without the zinc sulfate supplement. However, the data also revealed that individuals consuming the zinc supplement had a higher incidence of adverse effects such as nausea and vomiting than those who did not consume the supplement (Houston, Haggard, Williford, Meserve, & Shewokis, 2001).

Another study summarized literature investigating the safety of zinc supplementation and its effect on the healing of pressure ulcers and lower extremity vascular ulcers (Gray, 2003). The conclusion was that there is some evidence that zinc supplements may be useful in facilitating healing of vascular ulcers if deficiencies were identified. A study within this review reported that because zinc deficiencies are rarely the only nutritional deficit in patients with chronic wounds that a combination nutritional supplement may be needed (Brewer, Leal, & Mihaldzic, 1966; Watkin & Waldron, 1981). The review article concluded that all patients with pressure or vascular ulcers would likely benefit from a nutritional assessment (Gray, 2003).

Although there is evidence supporting the critical role zinc plays in the wound healing process, many of the study findings were not statistically significant. Thus, additional research is

needed to determine the effect zinc supplementation has on various types of chronic wounds such as CVLUs before it is recommended as a therapeutic intervention.

Protein And Wound Healing

Protein is another nutrient important for efficient wound healing. Deficiencies in protein can prolong the inflammatory phase of the healing process and inhibit wound remodeling (MacKay & Miller, 2003). Recommendations are for healthy men ages 19 and older to consume 56 g/day of protein and healthy women ages 19 and older to consume 46 g/day of protein (Food and Nutrition Board, Institute of Medicine, National Academies & U.S. Department of Agriculture, National Agricultural Library, 2013).

Several studies reviewed examined the effects of increasing protein intake in patients with pressure ulcers and other types of chronic wounds (Chernoff, Milton, & Lipschitz, 1990; Lee, Posthauer, Dorner, Redovian, & Maloney, 2006). The Health Quality Ontario analysis also investigated the effects of increasing protein intake using tube feedings in patients with pressure ulcers and reported that a very high protein tube feeding with 25% of energy as protein compared to a high protein tube feeding with 16% of energy as protein resulted in greater reduction in ulcer area over time (Chernoff et al., 1990). In addition, a study by Lee, Posthauer, Dorner, Redovian, and Maloney (2006) investigated the effects of a 15g hydrolyzed protein supplement compared to a placebo in long term care residents with level II, III, IV pressure ulcers (Lee et al., 2006). Residents receiving the protein supplement had twice the rate of healing after eight weeks compared to residents taking the placebo (Lee et al., 2006).

A study by Legendr, Debure, Meaume, Lok, Golmard, and Senet (2006), examined the protein status of patients with CVLUs. They reported that many patients with CVLUs were

protein deficient which they hypothesized may prolong the inflammatory phase of wound healing causing poor healing outcomes and an increase in wound complications. Alternatively, they hypothesized that CVLU patients may have high metabolic demands due to chronic inflammation at wound sites leading to depleted protein reserves (Legendre et al., 2008). Either way, increasing protein intake in CVLU patients who are deficient may enhance healing.

Amino Acids And Wound Healing

The amino acids arginine and glutamine are particularly important to the wound healing process. Amino acids are the building blocks of proteins and are essential in the daily human diet because human bodies cannot store excess amino acids as they can other nutrients (Escott-Stump, 2008; Trumbo, Schlicker, Yates, & Poos, 2002). Arginine is essential for tissue repair and immune function, and glutamine facilitates cell proliferation and provides a source of energy for inflammatory cells (MacKay & Miller, 2003). Arginine is considered a conditional amino acid, which means that in times of stress or illness it has to be obtained from the diet because the body cannot produce adequate amounts (Escott-Stump, 2008; Trumbo et al., 2002). Glutamine is considered a nonessential amino acid because it can be produced by the body. Because both arginine and glutamine are produced by the body there are no national guidelines for daily intake levels (Escott-Stump, 2008)

One study reviewed evaluated the effects of amino acids on healing rates of pressure ulcers in hospitalized acute care patients with stage II, III, or IV chronic pressure ulcers (Wong et al., 2012). Patients were randomized to receive either a specialized amino acid mixture supplement containing beta-hydroxy-beta-methylbutyrate, L-arginine, and L-glutamine and standard oral nutritional supplements or only the standard oral nutritional supplements for 2-4 weeks. Contents

of the standard nutritional supplement were not specified. While there was no significant difference in wound size over time between the two groups, the proportion of viable tissue was significantly increased in the treatment group. The authors concluded that adding specialized amino acids to diets of pressure ulcer patients may improve tissue viability in the long-term (Wong et al., 2012).

Although there is some evidence suggesting that oral supplements containing arginine and glutamine may be beneficial to wound healing in some circumstances, more research is needed before standard recommendations can be made.

Combinations Of Nutrient Supplements And Wound Healing

While there is evidence supporting the use of specific supplements to facilitate healing of chronic wounds, there are other data suggesting that a combination of nutrients is more beneficial. For example, Desneves, Todorovic, Cassar, and Crowe assessed the effects of adding 500mg/d of vitamin C, 9g/d of arginine, and 30mg/d of zinc to standard hospital diets on pressure ulcer healing compared to the effects of the standard hospital diet alone (Desneves et al., 2005). After three weeks there were significantly higher rates of pressure ulcer healing for the treatment group when compared to the control group. The data also revealed that patients with pressure ulcers had greater energy and protein requirements than other bed-bound patients and below RDI levels of zinc and albumin (Desneves, Todorovic, Cassar, & Crowe, 2005).

Similarly, in another study, patients with pressure ulcers were given high doses of vitamin C and zinc and a supplement containing protein, and arginine (exact amounts not provided) (Ellinger & Stehle, 2009). The authors concluded that this intervention may prevent the development of pressure ulcers (Ellinger & Stehle, 2009). The Heyman, Van De Looverbosch,

Meijer, and Schols study investigated whether an oral nutritional supplement of 575mg/d of vitamin C, 46 g/d protein, 69 g/d arginine, 87 mg/d vitamin E, and 21 mg/d zinc would improve the healing of pressure ulcers (grades II-IV) in nursing home residents (Heyman et al., 2008). A significant reduction in mean pressure ulcer area was reported at nine weeks when compared to baseline wound measurements (Heyman et al., 2008).

Studies by Delmi (1990), Houwing (2003), and (Hartgrink, 1998) investigated the effects of combination nutritional supplementation compared to hospital diet alone on the incidence of pressure ulcers in patients with hip fractures (Delmi et al., 1990; Hartgrink, Wille, Konig, Hermans, & Breslau, 1998; Houwing et al., 2003). The Delmi study assessed older adults for up to six months post-surgery and evaluated the number of pressure ulcers that developed in one group receiving a nutritional supplement daily (contents not described) in addition to the standard hospital diet and a control group receiving only the standard hospital diet (Delmi et al., 1990). The number of pressure ulcers that developed in the treatment group was lower than in the control group. Hartgrink (1998) compared the pressure ulcer risk between an intervention group receiving a standard hospital diet and nasogastric tube feedings consisting of 1 L Nutrison Steriflo Energy-plus (1500kcal/1 energy, 60 gram/1 protein) for two weeks to a control group receiving the standard hospital diet alone (Hartgrink et al., 1998). Although the data revealed that the pressure ulcer risk was lower for the treatment group when compared to the control group, the difference was not statistically significant (Hartgrink et al., 1998). Finally, Houwing et al. studied the effects of adding a supplement enriched with protein, arginine, zinc, and antioxidants to diets of patients with hip fractures on the incidence of pressure ulcers compared to a placebo group (Houwing et al., 2003). While the incidence of pressure ulcers was not different between the groups, the findings suggested that nutritional supplementation initiated early in the

hospitalization may be an effective approach for preventing pressure ulcers in hip fracture patients (Houwing et al., 2003).

Another study reviewed investigated the use of combination nutritional support on pressure ulcer healing (van Anholt et al., 2010). In this study, non-malnourished patients with stage III and IV pressure ulcers were given an oral supplement with 250kcal, 28.4g/d carbohydrates, 20g/d protein including 3g/d of arginine, 7g/d fat, 238mg/d vitamin A, 250mg/d vitamin C, 38mg/d vitamin E, 9mg/d zinc, 1.5mg/d carotenoids, 64micrograms/d selenium, 1.35mg/d copper, and 200micrograms/d folic acid for a maximum of eight weeks or a placebo for a maximum of eight weeks. A significantly greater decrease in pressure ulcer size was noted in the supplement group compared to the placebo group. The data also indicated that this type of supplement may reduce wound care costs by decreasing nursing time and accelerating wound healing (van Anholt et al., 2010). Similarly, a study by Ek et al. (1991) evaluated the effects of a high protein, high calorie, vitamin and mineral-enriched liquid supplement for 26 weeks on the development and healing of pressure ulcers (Ek, Unosson, Larsson, Von Schenck, & Bjurulf, 1991). Greater healing rates in the group taking the combination supplement compared to the control group receiving a standard diet were reported. Likewise, a study by Benati et al. assessed effects of a high protein, high calorie supplement enriched with arginine, zinc, vitamins A, C, and E and antioxidants added to the standard hospital diet of pressure ulcer patients and reported more healing when compared to those consuming just the standard hospital diet (Benati, Delvecchio, Cilla, & Pedone, 2001).

Although the collective studies reviewed suggest that multi-nutrient supplementation improves wound healing, more studies are needed using larger diverse samples to delineate the nutrient combinations, doses, and duration of supplementation.

Polyunsaturated Fatty Acids And Wound Healing

Polyunsaturated fatty acids (PUFAs) assist in regulating systemic and local inflammation and therefore likely influence the initial inflammatory stage of wound healing (Simopoulos, 2008). Generally speaking, n-3 PUFAs have strong anti-inflammatory and inflammation resolving actions, while n-6 PUFAs have greater pro-inflammatory effects (Simopoulos, 2008). It has been hypothesized that diets consisting of higher amounts of n-6 PUFAs relative to n-3 PUFAs prolong the inflammatory stage of wound healing and thus prevent or delay subsequent healing stages. The recommended optimal ratio of n-6 to n-3 PUFAs is ~4:1 to 1:1 (Simopoulos, 2008).

Eicosapentaenoic acid (EPA) and docosaheaenoic acid (DHA) are n-3 PUFAs specifically associated with anti-inflammatory effects and improvements in inflammatory conditions such as cardiovascular disease and rheumatoid arthritis (Simopoulos, 2008). Relative to wound healing, EPA and DHA generate lipid mediators (eicosanoids) that inhibit the migration of excessive levels of neutrophils to inflamed sites and reduce cell synthesis and secretion of pro-inflammatory cytokines (McDaniel et al., 2011). Conversely, arachidonic acid (AA) is an n-6 PUFA that generates lipid mediators that increase production of signaling proteins and interleukins that promote inflammation (Simopoulos, 2008). Thus the n-6 AA/n-3 EPA ratio is an important indicator of inflammatory status (McDaniel et al., 2011). Furthermore, manipulating the AA/EPA ratio with EPA supplements may be one way to reduce inflammation and promote the healing of chronic wounds that are “stuck” in the inflammatory stage.

McDaniel, Massey, and Nicolaou studied the effects of an oral EPA/DHA supplement on plasma AA/EPA ratios in healthy, young adults with acute wounds (McDaniel et al., 2011). Participants were given either 1.6g/d of EPA and 1.2 g/d of DHA or a placebo (2.3ml/d mineral

oil) for eight weeks. The data revealed that increasing EPA and DHA intake through oral supplementation resulted in significantly lower AA/EPA ratios in the active group when compared to baseline ratios and when compared to AA/EPA ratios in the placebo group at eight weeks. The authors concluded that balancing the AA/EPA ratio with n-3 EPA supplementation may reduce systemic and local inflammation and thus create a microenvironment in chronic wounds that is more conducive to healing (McDaniel et al., 2011).

Overall, the collective studies reviewed reported that dietary supplementation with certain nutrients may aid chronic wound healing. However, many of the studies reviewed has limitations such as small sample sizes, short study durations, diverse study methodologies, and variable patient populations making definitive conclusions difficult. Additionally, no studies reviewed focused exclusively on characterizing the nutrient intake of CVLU patients or the effects of dietary supplementation on CVLU healing.

III. Methodology

Research Design

This descriptive, cross-sectional study used secondary analysis of data to answer the research questions. The parent study's primary aim was to profile lipid mediators of inflammation in the microenvironment of CVLUs. One group of participants with CVLUs were studied at one time point after eligibility screening, informed consent, and enrollment.

The current study used the parent study's food frequency questionnaire (FFQ) data to determine the average daily intake levels of vitamin C, zinc, protein, select amino acids, and plasma PUFA data to determine average n-6 to n-3 ratios in patients with CVLUs. Socioeconomic data and opinions about nutritional supplements were also analyzed.

Population Sample

Data from a total of 12 adults with CVLUs, ages 48-80 years, from Central Ohio were included in the analysis. In the parent study, potential subjects were identified by reviewing medical records from the Comprehensive Wound Center. Participants were also recruited through advertisements placed on bulletin boards, in newspapers and other wound clinics in the Central Ohio area. The parent study was approved by an Institutional Review Board (IRB) and conducted in compliance with the ethical rules for human experimentation as stated in the 1975 Declaration of Helsinki.

Inclusion Criteria.

- CVLU between the ankle and knee for at least 3 months treated with compression therapy
- Ankle Brachial Pressure Index (ABPI/ABI) of ≥ 0.8
- Target wound of 8 cm^2 to 20 cm^2
- English speaking and ability to sign own consent

Rationale for inclusion criteria: A CVLU ≥ 3 months indicates chronicity. Compression therapy is the gold standard for CVLU treatment. An ABPI ≥ 0.8 confirms diagnosis of venous ulcer. It may be difficult to obtain adequate fluid from smaller wounds (< 8 cm^2) for the planned analyses. It is more likely that subjects who understand English will comprehend the study requirements than those who do not. The subject's ability to sign their own consent will provide assurance that they want to participate.

Exclusion Criteria.

- Allergy to fish or seafood
- Exposed bone, tendon, or fascia around the target wound
- Receiving anti-coagulants
- Immunologic related health problems, chronic inflammatory skin diseases, or diabetes mellitus if Hemoglobin A1C ≥ 7

- Taking non-steroidal anti-inflammatory drugs > 2x/week, nutritional supplements, or cortiocosteroids
- Chronic renal insufficiency
- Already in a study related to CVLU

Rationale for exclusion criteria: Supplements contain fish oil. There are additional healing complications when bone, tendon, or fascia are involved. Though some studies report that fish oil supplementation does not increase the risk of abnormal bleeding when administered concomitantly with warfarin other studies report decreases in coagulation when fish oil supplementation is added to warfarin therapy (Buckley, Goff, & Knapp, 2004) (Eritsland, Arnesen, Seljeflot, & Kierulf, 1995) (Keck Jr. et al., 2006). Immunological related conditions, inflammatory skin diseases, anti-inflammatory drugs, nutritional supplements, corticosteroids, and chronic renal insufficiency may affect one or all outcome measures. Uncontrolled diabetes often leads to a chronic inflammatory skin disease. Multiple study protocols may conflict.

Protocol (Parent Study)

After eligible individuals expressed interest in the study, a confidential screening interview was performed to confirm eligibility. Then, the appointment was scheduled at the Clinical Research Center (CRC) at The Ohio State University. Participants were instructed to consume only clear fluids during the 8 hours prior to their appointment to fulfill requirements for plasma PUFA assays. When participants arrived at the CRC for the appointment, the study requirements were reviewed and a consent form was presented for signature. Sociodemographic and nutritional supplement data were collected via a paper/pencil questionnaire that was completed by all participants. Body mass index (BMI) was calculated by CRC nurses. Blood was collected to measure plasma PUFA levels. Study participants were then instructed by the CRC bio

nutritionists to complete an electronic FFQ that collected data about nutrient intake from foods for the previous 90 days.

Instruments

Anthropometric Data. Height, weight, and BMI were calculated by the CRC nurses. Height was measured using the Harpendon Stadiometer (Holtain Limited, Crymych, Dyfed, U.K.) to the nearest 0.1 cm. Body weight was measured using the ProPlus Scale (Healthometer, Bridgeview Illinois) to the nearest 0.1 kg. BMI was calculated as body weight (kg) divided by height (m) squared.

Socio-demographic data. Participants completed a health and lifestyle questionnaire (teleform) wherein they self-reported gender, age, income level ($0 to 4,999; $5,000 to 9,999; $10,000 to 14,999; $15,000 to 19,999; $20,000 to 24,999; $25,000 to 29,999; $30,000 to 34,999; $35,000 to 39,999; $40,000 to 44,999; and $45,000 and up), years of education (less than 7 years, junior high school, some high school, high school, some college, college or university graduate [Bachelors or equivalent], and graduate or professional training [Masters, JD, MD, PhD, etc.]), marital status, race/ethnicity, occupation/employment, smoking status, stress level, nutritional supplements currently taking, and opinions about taking nutritional supplements to improve wound healing.

Food Frequency Questionnaire data. Nutritional intake data were collected using an electronic form of the FFQ validated by the Women's Health Initiative (Patterson et al., 1999). It is a web-based system that allows participants to administer the questionnaire to themselves on a tablet via internet connection. Participants received five minutes of audio and visual instruction before completing the FFQ, which takes approximately 30 minutes to complete and

asks questions about the type, frequency, and quantity of foods and beverages consumed in the past 90 days. The CRC bio nutritionists were available to assist participants as needed on the questionnaire. Once completed, the FFQ generates data including nutrient analysis of macro and micro nutrients consumed per day, food patterning, and an educational report for subjects. The dietary analysis was completed by the CRC bio nutritionists and utilized nutrient information from the Nutritional Coordinating Center (NCC) Food and Nutrient Database developed and maintained by the NCC, located at the University of Minnesota Division of Epidemiology and Community Health in Minneapolis.

Plasma PUFA levels. Plasma PUFA levels were quantified using gas chromatography/mass spectrometry (GC/MS) at Dr. Belury's laboratory at the College of Education and Human Ecology, OSU (Columbus, OH). Lipids were extracted from RBC and plasma samples with 2:1 (v/v) chloroform: methanol and 0.24ml 0.88% KCL (Folch, Lees, & Sloane-Stanley, 1957). Fatty acid methyl esters were prepared using tetramethylguandine at 100°C (Shantha, Decker, & Hennig, 1993). Fatty acid methyl esters were analyzed by gas chromatography using a 30-m Omegawax ™ 320 (Supelco-Sigma) capillary column. Oven temperature was started at 175°C and increased at a rate of 3°C/min until reaching 220°C. Flow rate of the carrier gas helium was 30mL/min. Retention times were compared to standards for fatty acid methyl esters (Supelco-Sigma, St. Louis, MO and Matreya, Inc., Pleasant Gap. PA). Fatty acids were reported as percent area of total fatty acids identified in plasma samples.

Data Analysis

Descriptive statistics, including percent, range, mean, and standard deviation (SD), were used to characterize socio-demographic, nutritional, plasma PUFA and body composition data.

IV. Research Results

Participant Characteristics. This secondary analysis compiled data on 12 adults, ages 48-80 years, from Central Ohio with a history of at least one CVLU for ≥ 3 months who were receiving standard compression therapy. In this sample, the majority of participants were older adult, Caucasian males (*M* = 64.25 years, *SD* = 9.49) (Table 1). On average participates had high BMI's (*M* = 41.48, *SD* = 11.47). The majority of participants had 12 years of education (58%), with 25% having had some college education and 16.7 % college or university graduates. Income levels varied, with 42% of participants falling below the federal poverty guideline, depending on the number of members in the household, with annual incomes at or below $15,000 (U.S. Department of Health and Human Services, 2014). Additionally, 25% of participants had an average annual income $15,000-29,999, 8% had an average annual income $30,000-44,999, and 25% had an average annual income of $45,000 or more. On average the Perceived Stress Scale scores were midlevel (*M* = 16.42, *SD* = 9.80), with 50% of participants scoring a 20 or higher. PSS scores range from 0-40 with higher PSS scores indicating higher levels of perceived stress. All participants (100%) stated they would consider taking a dietary supplement prescribed to improve wound healing with cost and side effects the primary factors affecting this decision.

Table 1. Socio-demographic data (n=12)

	Number in sample (SD)
Age, mean years	64.25 (9.49)
Age, range	48-80
Gender:	
Male	10
Female	2
Race:	
Caucasian	8
African American	3
Other	1 (Creole)
Education:	
High school graduate	7
Some college	3
College/University graduate	2
Annual household income:	
< $10.000	4
$10,000 - $14,999	1
$15,000 - $29,999	3
$30,000 - $44,999	1
$45,000 or more	3
BMI, kilograms/meter^2, mean	41.48 (11.47)
PSS score, mean	16.42 (9.80)
Consider making dietary changes/taking supplements	12 (100%)

Mean (SD) all such values
BMI= body mass index
PSS= Perceived Stress Scale (0-40) with higher score=higher perceived stress

Food Frequency Questionnaire data. The VioFFQ (VIOcare Technologies, Inc.) indicated on average, a low daily intake of vitamin C (*M* = 60.03 mg/day, *SD* = 49.73), a normal daily intake of zinc (M = 10.78mg/day, SD = 5.17), a normal daily intake of protein (*M* = 71.37g/day, *SD* = 31.32), a high intake of glutamic acid (*M* = 13.79g/day, *SD* = 5.89), a high intake of arginine (*M*

= 3.74 g/day, *SD* = 1.75), low intake of EPA (*M* = 0.027 g/day, *SD* = 0.021), low intake of DHA (*M* = 0.064 g/day, *SD* = 0.047), low intake of EPA+DHA (*M* = 0.046 g/day, *SD* = 0.034), and an intake of AA (*M* = 0.17 g/day, *SD* = 0.16). Details of these values can be seen in Table 2.

Table 2. Food Frequency Questionnaire data (n=12)

Nutrient	FFQ Results Mean (SD)	RDI
Vitamin C, mg/day	60.03 (49.73)	75-90
Zinc, mg/day	10.78 (5.17)	8-11
Protein, g/day	71.37 (31.32)	46-56
Amino Acid		
Glutamic Acid, g/day	13.79 (5.89)	0.8g/kg body weight/day*
Arginine, g/day	3.74 (1.75)	0.4-1.0 **
PUFA		
EPA,g/day	0.027 (0.021)	0.4-0.5 EPA&DHA***
AA, g/day	0.17 (0.16)	N/A
DHA, g/day	0.064 (0.047)	0.4-0.5 EPA&DHA***

RDI= Recommended Daily Intake
*Recommended Daily Allowance
** Tolerable Upper Limit
*** No individual RDI
DHA= docosahexaenoic acid
EPA= eicosapentaenoic acid
AA= arachidonic acid

Plasma PUFA data. The average n-6:n-3 PUFA ratio for the group was 11.25:1 (*M* = 11.25, *SD* = 1.99). The average plasma AA was 8.64% (*M* = 8.64, *SD* = 2.79), plasma EPA was 0.43% (*M* = 0.43, *SD* = 0.14), and plasma DHA was 2.14% (*M* = 2.14, *SD* = 0.66).

Table 3. Plasma PUFA data (n=12)

PUFAs % of total	**Plasma Mean (SD)**	Normal Range
n-6:n-3	11.25 (1.99)	4:1 (optimal)
EPA	0.43 (0.14)	
AA	8.64 (2.73)	
DHA	2.14 (0.66)	

EPA= eicosapentaenoic acid
AA= arachidonic acid
DHA= docosahexaenoic acid

V. Summary, Conclusion, and Implications

Summary Of Findings

The main purpose of this study was to characterize the nutrient intake patterns of a sample of participants with CVLUs. The focus was on vitamin C, zinc, protein, amino acids, and PUFAs, as well as, blood plasma PUFA levels because these nutrients are known to affect wound healing. The study results indicate that the participants consumed adequate amounts of zinc and protein according to RDI parameters; however, vitamin C and EPA + DHA consumption was below the RDI levels. These findings of low vitamin C intake levels are in alignment with previous studies reporting that many patients with acute wounds, such as pressure ulcers, are vitamin C deficient (Gray & Whitney, 2003). The findings that the sample were consuming adequate amounts of zinc and protein were not in accord with previous studies reporting that many pressure ulcer patients have zinc and protein deficiencies (Health Quality Ontario, 2009) and that CVLU patients are often protein deficient (Legendre et al., 2008).

The current study data also indicated that participants consumed above the recommended daily allowance of glutamic acid and above the tolerable upper intake level of arginine.

Conversely, the combined daily intake of EPA + DHA was found to be below the RDI. Additionally, blood plasma PUFA data indicated that on average participants had a high n-6/n-3 PUFA ratio compared to the reported optimal ratio.

We also report that the majority of participants (81.8%) were classified as obese. Obesity has been associated with increased systemic inflammation as well as increased risk for various chronic diseases including cardiovascular disease and diabetes mellitus, which are predisposing factors for wound formation (National Institutes of Health, 2014). Additionally, 42% percent of participants reported an annual income at or below the federal poverty guidelines (at or below $15,000) (U.S. Department of Health and Human Services, 2014), which could be impacting their ability to purchase healthy, nutrient rich foods.

This study's findings indicate that some CVLU patients are not consuming adequate amounts of certain key nutrients needed for efficient wound healing, which agree with others reporting that patients with chronic wounds are often nutritionally deficient in more than one nutritional category (Brewer et al., 1966). The CVLU patients in the sample were also consuming excessive amounts of nutrients known to prolong inflammatory processes (n-6 PUFAs), which could be contributing to healing delays. Furthermore, the participants may be at increased risk for poorer overall health outcomes because of their low socioeconomic status and high BMIs. Finally, the study findings suggest that the increased perceived stress levels for some CVLU patients could be contributing to wound healing delays because higher levels of stress have been associated with slower wound healing (Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998).

Conclusions

In summary, while the study participants were consuming adequate levels of certain key nutrients essential for wound healing, their intake of other key nutrients were either below or

above the recommended levels. These findings indicate that it may be important for CVLU patients to have nutritional assessments to determine whether dietary changes or supplements should be recommended. The findings also show that the majority of the sample were morbidly obese and experiencing moderately high levels of stress in their lives. Promoting healthy, nutrient-rich diets and introducing ways to achieve a healthy weight and reduce stress may improve healing outcomes as well as the overall health of this patient population.

Implications For Practice

A patient-centered, multidisciplinary, holistic approach that includes a dietary assessment and nutritional counseling may improve healing outcomes and the overall health of CVLU patients. Nurses are important members of the healthcare team who can facilitate communication among the stakeholders so that the most current evidence based care can be provided to this population of patients.

Recommendations

Additional research is needed to validate the findings of this study in a larger, more diverse patient population. It will also be important for future studies to determine the effects of certain nutritional interventions on CVLU healing, such as balancing high n-6/n-3 ratios with n-3 PUFA supplementation and include potential socioeconomic barriers to consuming healthy foods.

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